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Impacts of air pollution and noise on risk of preterm birth and stillbirth in London

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ABSTRACT

Background: Evidence for associations between ambient air pollution and preterm birth and stillbirth is inconsistent. Road traffic produces both air pollutants and noise, but few studies have examined these co-exposures together and none to date with all-cause or cause-specific stillbirths.
Objectives: To analyse the relationship between long-term exposure to air pollution and noise at address level during pregnancy and risk of preterm birth and stillbirth.
Methods: The study population comprised 581,774 live and still births in the Greater London area, 2006–2010. Outcomes were preterm birth (< 37 completed weeks gestation), all-cause stillbirth and cause-specific stillbirth. Exposures during pregnancy to particulate matter with diameter < 2.5 µm ($PM_{2.5}$) and < 10 µm (PM_{10}), ozone (O_3), primary traffic air pollutants (nitrogen dioxide, nitrogen oxides, $PM_{2.5}$ from traffic exhaust and traffic non-exhaust), and road traffic noise were estimated based on maternal address at birth.
Results: An interquartile range increase in O_3 exposure was associated with elevated risk of preterm birth (OR 1.15 95% CI: 1.11, 1.18, for both Trimester 1 and 2), all-cause stillbirth (Trimester 1 OR 1.17 95% CI: 1.07, 1.27; Trimester 2 OR 1.20 95% CI: 1.09, 1.32) and asphyxia-related stillbirth (Trimester 1 OR 1.22 95% CI: 1.01, 1.49). Odds ratios with the other air pollutant exposures examined were null or < 1, except for primary traffic non-exhaust related $PM_{2.5}$, which was associated with 3% increased odds of preterm birth (Trimester 1) and 7% increased odds stillbirth (Trimester 1 and 2) when adjusted for O_3. Elevated risk of preterm birth was associated with increasing road traffic noise, but only after adjustment for certain air pollutant exposures.
Discussion: Our findings suggest that exposure to higher levels of O_3 and primary traffic non-exhaust related $PM_{2.5}$ during pregnancy may increase risk of preterm birth and stillbirth; and a possible relationship between long-term traffic-related noise and risk of preterm birth. These findings extend and strengthen the evidence base for important public health impacts of ambient ozone, particulate matter and noise in early life.

1. Introduction

There is strong evidence that exposure to ambient air pollution during pregnancy is associated with increased risk of infant mortality and reduced birth weight (Lacasana et al., 2005; Sun et al., 2016), but evidence for associations with preterm birth (PTB) and stillbirth is less consistent (Klepac et al., 2018; Siddika et al., 2016). Road traffic is a major contributor to air pollution, especially in urban areas, but it is

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also a source of noise. Adverse health effects associated with road traffic noise, independent of air pollution, include hypertension and cardiovascular outcomes (Kempen et al., 2018; Stansfeld, 2015), thus noise could plausibly affect PTB and stillbirth. Potential biological mechanistic pathways are oxidative stress and systemic inflammatory responses for air pollution (Kelly, 2003; Vadillo-Ortega et al., 2014), and stress responses for noise (Nieuwenhuijsen et al., 2017), leading to e.g. disrupted placental function, and thus adverse birth outcomes. Ozone (O_3) is a secondary toxic air pollutant, the distribution of which is highly influenced by traffic-related air pollution in urban areas, because close to nitrogen oxide (NO_X) sources such as road traffic, O_3 is titrated out by NO_X and thus decreased.

In England and Wales in 2016, 8.1% of all births were preterm and the stillbirth rate was 4.4 per 1000 total births (ONS, 2017). PTB is a leading direct cause of neonatal death, and is associated with increased morbidity and long-term sequelae (Lawn et al., 2010). Failure to account for road traffic noise co-exposures could contribute to heterogeneity of findings for air pollution in relation to PTB and stillbirth in previous research (Klepac et al., 2018; Siddika et al., 2016). Air pollution and noise have been investigated jointly in relation to PTB in four study populations with conflicting results (Arroyo et al., 2016; Barba-Vasseur et al., 2017; Dzhambov et al., 2019; Gehring et al., 2014), but not in relation to stillbirth. This study investigates long-term exposure to traffic-related air pollution and noise, and O_3 during pregnancy and risk of PTB and, for the first time also, all-cause and cause-specific stillbirth.

2. Materials and Methods

2.1. Births data

All births (N = 687,147) occurring during 2006–2010 to mothers residing within middle layer super output areas (MSOAs) completely within the M25 were extracted from the UK National Births/Stillbirth registers supplied by the Office for National Statistics (ONS). A map of the study area has been published elsewhere (Smith et al., 2017). The M25 is an orbital motorway surrounding Greater London (2317 km^2). These registers provide routine data on all live and stillbirths (legally defined in the UK as born after 24 completed weeks gestation showing no signs of life) in the UK, including birth weight, sex, maternal age, maternal residential address at birth, and Wigglesworth stillbirth cause of death codes classified by ONS (Dattani and Rowan, 2002). Gestational age and infant ethnicity were appended from the NHS Numbers for Babies (NN4B) dataset, with 99% linkage. Gestational age assessment is likely to be based on routine second trimester scans, although some may be based on last menstrual period (Moser and Hilder, 2008). Preterm birth was defined as < 37 completed weeks gestation.

We geocoded maternal residential addresses using QuickAddress Software (0.1 m accuracy) (Experian Ltd, 2015). Information on maternal residential mobility during pregnancy was not available. We appended the following 2011 census output area (COA)-level data: Carstairs deprivation index from the UK Census 2011 standardised across COAs in the study area (Carstairs and Morris, 1990); and, as a smoking proxy, 2014 tobacco expenditure (GBP) per week per person (population ≥16 years) from CACI Ltd.

2.2. Exposure assessment

The air pollution and noise modelling and exposure assessment are described in detail elsewhere (Smith et al., 2017). Average monthly concentrations of nitrogen dioxide (NO_2), NO_X, O_3, particulate matter with diameter < 2.5 μm ($PM_{2.5}$) and < 10 μm (PM_{10}), $PM_{2.5}$ from traffic exhaust ($PM_{2.5\ traffic\text{-}exhaust}$) and traffic non-exhaust ($PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ = brake/tyre wear particles and resuspension of road dust) were estimated for 20x20m regular grid points across the study area, using dispersion modelling (KCLurban) (Beevers et al., 2013). NO_2, NO_X, $PM_{2.5\ traffic\text{-}exhaust}$ and $PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ are primary traffic-related pollutants (i.e. locally emitted/rapidly formed near-source oxidation products). O_3 is a secondary pollutant, which in London varies inversely with NO_2 and NO_X due to titration, meaning it tends to be lowest around major roads and highest in residential areas. $PM_{2.5}$ and PM_{10} are more homogeneously distributed than primary traffic-related pollutants. $PM_{2.5}$ and PM_{10} include particles from primary traffic sources, but are mostly dominated by regional/long-range particles and secondary particles formed through atmospheric chemical reactions. The KCLurban model uses Atmospheric Dispersion Modelling System v4 and road source model v2.3; data on emissions from the London Atmospheric Emissions Inventory (LAEI);(Greater London Authority (GLA) 2010) empirically derived NO-NO_2-O_3 and PM relationships; and hourly meteorological information (Beevers et al., 2013). Model predictions show good agreement with the observations across measurement site types and seasonality (spearman correlation coefficients (r) between observed vs modelled monthly concentrations: $r > 0.91$ for NO_X, PM_{10} and $PM_{2.5}$, $r > 0.83$ for NO_2 and $r > 0.9$ for O_3 at both roadside and background locations) (Beevers and Dajnak, 2015), providing robust metrics for subsequent analysis. Normalised mean bias (NMB) for modelled monthly predictions were as follows: NO_X (NMB = 11%), NO_2 (NMB = 11%), $PM_{2.5}$ (NMB = 5%), PM_{10} (NMB = 6%) and O_3 (NMB = −13%). $PM_{2.5}$ and PM_{10} were predicted slightly more accurately than NO_2 and NO_X and O_3, but for all these pollutants model bias was in the same direction (over-prediction), except for O_3 which under-predicted (reflecting the positive NO_2 bias). Each maternal address was assigned monthly air pollutant concentrations for the nearest 20x20m grid point. Time-weighted averages were calculated for whole pregnancy, trimesters, and last 3 months of pregnancy. Day 1 of pregnancy was calculated by converting 'completed' gestation weeks to days, adding 4 days (to adjust for underestimation as true gestation may not be an exact number of completed weeks), and subtracting from date of birth. However, initial examination of functional air pollutant–outcome relationships indicated that whole pregnancy, Trimester 2 and Trimester 3 average air pollutant exposures demonstrated U-shaped functional relationships with outcomes, that were not present for average exposures over fixed length time periods (i.e. Trimester 1 and last 3 months preceding birth). We found that this was due to the strong seasonal pattern in our modelled air pollutants combining with shorter average gestational age for cases vs non-cases for both PTB and stillbirth. This meant that average exposures for those with shorter gestations were more strongly influenced by seasonal peaks and troughs, and thus more likely to be further above or further below the mean in the exposure distribution, than those with longer gestation periods, resulting in U-shaped functional relationships. We therefore limited the analysis to Trimester 1, Trimester 2 (but restricted to births occurring at ≥186 days, i.e. having full length Trimester 2), and last 3 months of pregnancy air pollution exposures, to avoid bias associated with mean gestation being shorter for preterm vs term births, and still vs live births. Last 3 months exposure was not analysed for preterm birth, as this outcome is a function of gestational age, and thus the underlying biological time window it represents would clearly be different for preterm vs term births. Analysis of last 3 months of pregnancy exposure was analysed only for stillbirth, and further restricted to term births (i.e. 37 weeks gestation) in sensitivity analyses to achieve greater comparability in terms of the biological time window for cases vs non-cases.

A-weighted sound pressure levels from road traffic, specifically annual average $L_{Aeq,16hr}$ (0700–2300 h); L_{night} (2300–0700); L_{day} (0700–1900); L_{eve} (1900–2300); and L_{den} (composite of L_{day}, L_{eve}, and L_{night} with a 5 dB(A) penalty added to the L_{eve} and 10 dB(A) penalty added to L_{night}), were modelled to 0.1 dB(A) resolution for all maternal residential addresses (1 m from the façade on the side of the dwelling closest to the nearest road section with traffic information) using the TRAffic Noise EXposure (TRANEX) model (Gulliver et al., 2015). We modelled noise for a single year (2007) and applied these values to

Table 1
Characteristics of the study population.

Characteristic	N for PTB analysis (live births only)	N PTB cases (%[b])	N for stillbirth analysis (live and still births)	N stillbirth cases (%[c])
Total population	578,382	33,712 (5.83)	581,774	3392 (0.58)
Infant sex				
Male	296,356	18,390 (6.21)	298,181	1825 (0.61)
Female	282,026	15,322 (5.43)	283,593	1567 (0.55)
Maternal age				
< 25	108,324	6762 (6.24)	108,999	675 (0.62)
25–29	149,696	8295 (5.54)	150,493	797 (0.53)
30–34	180,684	9722 (5.38)	181,637	953 (0.52)
≥35	139,678	8933 (6.4)	140,645	967 (0.69)
Ethnicity				
White	304,225	15,710 (5.16)	305,596	1371 (0.45)
Asian	100,681	6448 (6.4)	101,380	699 (0.69)
Black	99,790	7263 (7.28)	100,712	922 (0.92)
Other	73,686	4291 (5.82)	74,086	400 (0.54)
Birth registration				
Within marriage[a]	370,312	19,296 (5.21)	372,414	2102 (0.56)
Sole registration	39,464	3274 (8.3)	39,837	373 (0.94)
Joint/same address	113,008	6929 (6.13)	113,648	640 (0.56)
Joint/different address	55,598	4213 (7.58)	55,875	277 (0.5)
Season of conception				
Winter	147,318	8299 (5.63)	148,177	859 (0.58)
Spring	139,942	8748 (6.25)	140,768	826 (0.59)
Summer	142,995	8307 (5.81)	143,834	839 (0.58)
Autumn	148,127	8358 (5.64)	148,995	868 (0.58)
Year of birth				
2006	108,732	6588 (6.06)	109,394	662 (0.61)
2007	114,137	6788 (5.95)	114,854	717 (0.62)
2008	114,507	6818 (5.95)	115,182	675 (0.59)
2009	117,689	6670 (5.67)	118,327	638 (0.54)
2010	123,317	6848 (5.55)	124,017	700 (0.56)
Carstairs quintile				
1 – least deprived	90,212	4163 (4.61)	90,614	402 (0.44)
2	97,970	4924 (5.03)	98,439	469 (0.48)
3	107,932	6216 (5.76)	108,548	616 (0.57)
4	128,051	7876 (6.15)	128,894	843 (0.65)
5 – most deprived	154,217	10,533 (6.83)	155,279	1062 (0.68)
Tobacco expenditure quintile				
1	117,052	5815 (4.97)	117,648	596 (0.51)
2	117,251	6265 (5.34)	117,884	633 (0.54)
3	117,126	6825 (5.83)	117,822	696 (0.59)
4	117,937	7487 (6.35)	118,672	735 (0.62)
5	109,016	7320 (6.71)	109,748	732 (0.67)
London				
Inner	185,277	10,875 (5.87)	186,336	1059 (0.57)
Outer	393,105	22,837 (5.81)	395,438	2333 (0.59)

Note: PTB, preterm birth (< 37 completed weeks gestation).
[a] Includes civil partnerships.
[b] Denominator is live births.
[c] Denominator is live and still births.

other years for the same address locations as initial noise modelling had shown temporal variability over the study period was negligible. Noise could not be estimated for 4.5% of births due to address point (receptor) placement issues (Gulliver et al., 2015), however these addresses were randomly spatially distributed. TRANEX model validation studies demonstrated high correlation between model predictions and measured noise levels (Gulliver et al., 2015). Addresses exposed to > 50 dB(A) noise (L_{day}) from railways or aircraft (Heathrow and City Airports) were flagged. Railway and City Airport noise data were from Environmental Noise Directive strategic noise mapping (2006 annual average), and Heathrow Airport noise from annual average contours (2001) from the Civil Aviation Authority.

2.3. Exclusions

We restricted to singleton births, excluding 23,131 multiple births. We excluded births with gestational age < 24 weeks (N = 625, 0.1%) and > 44 weeks (N = 458, 0.1%) or missing data for gestational age (n = 9725, 1.5%), noise (N = 31,197, 4.7%), or ethnicity (N = 47,710, 7.2%) leaving 581,774 live and stillbirths. Analysis of PTB was restricted to 578,382 live births. Missing/extreme values exclusion counts are not mutually exclusive.

2.4. Statistical methods

Air pollutant and noise exposures were analysed as continuous measures rescaled to interquartile range (IQR) increments, in order that effect estimates could be compared for exposures with different

absolute ranges. We analysed one day-time ($L_{Aeq,16hr}$) and one night-time (L_{night}) metric, as all noise exposures were highly correlated. Noise metrics were right skewed so were additionally analysed as a categorical variable ($L_{Aeq,16hr}$ < 55 dB (reference), 55– < 60 dB, 60– < 65 dB, ≥65 dB; and L_{night} < 50 dB (reference), 50– < 55 dB, 55– < 60 dB, 60– < 65 dB, ≥65 dB). We analysed PTB and stillbirth using logistic regression (in Stata version 13). We also analysed 2 cause-specific stillbirth groups: congenital malformations (Wigglesworth code 1) and asphyxia/anoxia/trauma (Wigglesworth codes 4 and 8A) (Dattani and Rowan, 2002). The remaining cause-specific codes either contained insufficiently large numbers for robust analysis (antepartum infections – code 2, external conditions – code 5, other specific conditions – code 7) or did not constitute a meaningful homogeneous cause-specific group (other conditions – codes 0 and 8B) for analysis. All models were adjusted, *a priori*, for sex, maternal age (< 25, 25–29, 30–34 and ≥35); birth registration type (within marriage, joint-same address, joint-different address, sole registered), baby's ethnicity (White, Asian, Black, Other), tobacco expenditure, Carstairs deprivation quintile, season of conception, and year; and a random intercept for MSOA was included to account for underlying spatial patterns in the data from potentially unmeasured confounders. We further adjusted air pollutants for noise, and vice versa in joint-exposure models. We ran two-air-pollutant models for O_3 vs each of other air pollutants, assessing models on a case-by-case basis for collinearity by inspecting standard errors (i.e. if standard error more than doubled). We performed several sensitivity analyses: evaluating possible effect modification by ethnicity (exposure × ethnicity interaction term), deprivation (exposure × Carstairs quintile interaction term), Inner/Outer London (exposure × Inner/Outer London interaction term); excluding those exposed to higher railway/aircraft noise (> 50 dB); and stillbirth stratified by term/preterm. We also used generalized additive models (GAM) to evaluate non-linearity (in R version 3.1.2 mgcv package).

2.5. Ethical approval

The study uses SAHSU data - UK National Births and Stillbirth register data and NHS Numbers for Babies (NN4B), supplied by the Office for National Statistics (NN4B now taken over by NHS Digital and referred to as Birth Notifications Data). The study was covered by national research ethics approval from the London-South East Research Ethics Committee - reference 17/LO/0846. Data access was covered by the Health Research Authority - Confidentiality Advisory Group under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002- HRA CAG reference: 14/CAG/1039.

3. Results

The study population contained 33,712 preterm births (5.83%) and 3392 stillbirths (0.58%), and distributions of these outcomes according to population, temporal, and spatial characteristics are summarised in Table 1. Table 2 provides summary statistics for air and noise pollution exposures. Air pollutant exposures within the same time window were positively correlated (0.51–1.00), except with O_3 which was negatively correlated with all other air pollutants (−0.23 to −0.76) (Supplementary Table 1). Road traffic noise was positively correlated with air pollutant exposures (0.08–0.39) except O_3 (~−0.08). Prevalence of PTB and stillbirth, and mean air pollutant exposures (NO_2, NO_X, $PM_{2.5\ traffic\text{-}exhaust}$, $PM_{2.5}$, PM_{10}) decreased, and mean noise exposures increased in the population from 2006 to 2010 (Supplementary Tables 2 & 3). The latter must reflect changing spatial distribution of maternal residential addresses over time as noise modelling was not time-varying. Relationships between potential confounders and exposures and outcomes are shown in Supplementary Tables 2 and 3 respectively, and functional relationships between outcomes and exposures are shown in Supplementary Figs. 1 & 2.

In adjusted single-pollutant models, an IQR increase in Trimester 1 and Trimester 2 O_3 were both associated with 15% increased odds of PTB (OR 1.15 95% CI: 1.11, 1.18) and 17% and 20% increased odds of all-cause stillbirth respectively (Trimester 1 OR 1.17 95% CI: 1.07, 1.27; Trimester 2 OR 1.20 95% CI: 1.09, 1.32) (Tables 3 and 4), whereas other air pollutants in Trimester 1 or Trimester 2 were associated with ORs < 1.00 or no association. There were no associations between stillbirth and any air pollutant exposures during the last 3 months preceding birth (Table 4). Air pollutant ORs were virtually unchanged when adjusted for day- or night-time road traffic noise (Tables 3 and 4).

In single-exposure adjusted models, neither continuous nor categorical road traffic noise was associated with PTB or stillbirth (Table 5, Supplementary Table 4), and single-exposure adjusted GAMs were consistent with this (not shown). However, an IQR increase in road traffic noise was associated with 1–2% increased odds of PTB after adjustment for Trimester 1 NO_2, NO_X, $PM_{2.5\ traffic\text{-}exhaust}$, and PM_{10}, and Trimester 2 NO_2, NO_X, $PM_{2.5\ traffic\text{-}exhaust}$, $PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ and PM_{10}, in turn (Table 5). This appeared driven by elevated odds of PTB in the highest (≥65 dB) noise category, with a similar pattern observed for stillbirth in relation to noise ≥ 65 dB (Supplementary Table 4). In adjusted joint-exposure GAMs, associations for road traffic noise were generally consistent with results from logistic regression models for continuous road traffic noise, i.e. suggestive of small elevated risk of PTB associated with an IQR increase in noise, after adjustment for primary traffic-related air pollutants (NO_2, NO_X, $PM_{2.5\ traffic\text{-}exhaust}$, $PM_{2.5\ traffic\text{-}non\text{-}exhaust}$), but with little suggestion of associations with stillbirth. There was little indication of non-linear relationships with noise, nor of elevated risk associated with noise ≥65 dB specifically (Supplementary Figs. 3 and 4, only night-time noise shown).

In two-air-pollutant models for O_3 vs each of the other pollutants, Trimester 1 and 2 O_3 exposures were associated with elevated risk of PTB and stillbirth when adjusted for other air pollutants, except PM_{10} for Trimester 2 (PTB) and PM_{10} for Trimester 1 (stillbirth) (Tables 6 and 7). 'Protective' associations for PTB observed for Trimester 1 NO_2, NO_X or $PM_{2.5\ traffic\text{-}exhaust}$ were attenuated to null, and $PM_{2.5\ traffic\ non\text{-}exhaust}$ became associated with a small increased risk of PTB (OR 1.03, 95%CI: 1.01, 1.05), when adjusted for O_3. Other ORs for PTB were slightly attenuated by adjustment for O_3. Trimester 1 and 2 $PM_{2.5\ traffic\ non\text{-}exhaust}$ was also associated with a small increased risk for stillbirth (OR 1.07, 95%CI: 1.01, 1.13) when adjusted for O_3. Few 'protective' associations with stillbirth remained after adjustment for O_3 (only Trimester 1 $PM_{2.5}$ and PM_{10}). Associations between stillbirth and any air pollutant exposures during the last 3 months preceding birth remained null in two-air-pollutant models (Table 7).

There was generally some increase in the standard errors for the exposure terms in two-air-pollutant models, but not of a magnitude indicating multicollinearity.

Analysis of cause-specific stillbirth revealed Trimester 1 O_3 was associated with 22% (1–49%) increased odds of asphyxia-related stillbirth (similar OR for Trimester 2 O_3 but not reaching statistical significance). ORs < 1.00 were observed for asphyxia-related stillbirth in relation to Trimester 2 $PM_{2.5\ traffic\text{-}exhaust}$, $PM_{2.5}$ and PM_{10}, and for congenital malformations-related stillbirth in relation to Trimester 1 $PM_{2.5}$ and PM_{10}, but associations for all other air pollutant or noise exposures were null (Table 8). Air pollutant and noise associations were unchanged when further adjusted for noise and air pollutants respectively (not shown).

3.1. Sensitivity analyses

Results for Trimester 1 air pollutant exposures (and noise adjusted for Trimester 1 air pollutant exposures) were very similar when restricted to the subset for whom Trimester 2 air pollutant exposures were analysed (i.e. those with a full-length Trimester 2) (Supplementary Tables 5, 6, and 7). Associations between stillbirth and Trimester 1 and 2 air pollutants were similar when stratified term/preterm, and there

Table 2
Air pollution and road traffic noise exposures in the study population (N = 581,774).

Exposure	Mean	SD	Min	25th percentile	Median	75th percentile	Max	IQR
Air pollutants (Trimester 1 average) (μg/m^3)								
NO_2	41.1	9.9	15.8	33.5	40.1	47.6	186.5	14.0
NO_X	73.7	27.0	19.9	53.0	69.2	89.7	513.4	36.7
$PM_{2.5\ traffic\text{-}exhaust}$	0.63	0.30	0.11	0.42	0.57	0.77	7.60	0.35
$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$	0.73	0.32	0.13	0.51	0.68	0.89	7.10	0.38
$PM_{2.5}$	14.6	2.4	8.7	13.1	14.7	16.3	30.9	3.2
PM_{10}	23.6	3.1	12.3	21.5	23.5	25.5	50.8	4.0
O_3	31.1	11.4	0.0	22.9	30.7	40.5	60.3	17.6
Air pollutants (Trimester 2 average) (μg/m^3)								
NO_2	40.6	10.2	14.3	33.0	39.7	47.3	200.8	14.4
NO_X	72.6	27.3	16.8	51.7	68.3	89.0	581.2	37.3
$PM_{2.5\ traffic\text{-}exhaust}$	0.62	0.30	0.11	0.41	0.55	0.75	7.32	0.35
$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$	0.73	0.31	0.14	0.51	0.67	0.89	7.65	0.38
$PM_{2.5}$	14.5	2.5	8.7	12.7	14.6	16.3	28.6	3.6
PM_{10}	23.2	3.5	11.8	20.9	23.3	25.4	52.5	4.5
O_3	32.0	11.9	0.0	23.2	31.7	42.3	60.9	19.1
Air pollutants (Last 3 months average) (μg/m^3)								
NO_2	40.0	10.2	14.3	32.3	39.0	46.7	187.7	14.4
NO_X	71.1	27.3	16.7	50.3	66.5	87.3	539.3	37.0
$PM_{2.5\ traffic\text{-}exhaust}$	0.60	0.29	0.12	0.40	0.53	0.73	6.68	0.33
$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$	0.72	0.31	0.13	0.50	0.66	0.87	7.11	0.38
$PM_{2.5}$	14.2	2.5	8.6	12.2	14.3	15.9	29.7	3.6
PM_{10}	22.5	3.8	11.8	20.3	22.8	24.9	51.4	4.7
O_3	32.5	11.6	0.0	24.3	32.6	42.3	60.9	17.9
Noise (dB)								
$L_{Aeq,16hr}$	58.1	5.2	54.7	55.0	55.4	58.5	86.0	3.5
L_{night}	53.2	5.4	49.6	49.9	50.5	53.8	80.0	3.9
L_{day}	58.4	5.2	55.0	55.2	55.7	58.8	86.4	3.6
L_{eve}	56.9	4.9	53.7	54.0	54.4	57.1	84.4	3.1
L_{den}	59.8	5.2	56.3	56.6	57.1	60.3	86.7	3.7

Note: with the exception of maximum value for NO_2 Last 3 Months exposure, the summary statistics did not vary between the various subsets used in analysis, and are thus presented for the full study population here.

Table 3
Odds of preterm birth associated with air pollutant exposure, in single-exposure and joint air pollutant-noise exposure models (OR, 95% CI).

Exposure	Preterm birth Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted + day-time noise[b] OR (95% CI)	Adjusted + night-time noise[b] OR (95% CI)
Air pollutants (Trimester 1 average)				
NO_2 (per IQR, 14.0 μg/m^3)	0.97 (0.95, 0.98)	0.93 (0.90, 0.95)	0.92 (0.90, 0.94)	0.92 (0.90, 0.94)
NO_X (per IQR, 36.7 μg/m^3)	0.97 (0.95, 0.98)	0.93 (0.91, 0.95)	0.93 (0.91, 0.95)	0.93 (0.91, 0.95)
$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.35 μg/m^3)	0.99 (0.98, 1.00)	0.95 (0.94, 0.97)	0.94 (0.92, 0.96)	0.94 (0.92, 0.96)
$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	0.99 (0.98, 1.00)	0.97 (0.96, 0.99)	0.96 (0.95, 0.98)	0.96 (0.95, 0.98)
$PM_{2.5}$ (per IQR, 3.2 μg/m^3)	0.98 (0.96, 0.99)	0.93 (0.91, 0.95)	0.93 (0.91, 0.95)	0.93 (0.91, 0.95)
PM_{10} (per IQR, 4.0 μg/m^3)	0.95 (0.94, 0.97)	0.88 (0.87, 0.90)	0.88 (0.86, 0.90)	0.88 (0.86, 0.90)
O_3 (per IQR, 17.6 μg/m^3)	1.08 (1.06, 1.10)	1.15 (1.11, 1.18)	1.15 (1.12, 1.18)	1.15 (1.12, 1.18)
Air pollutants (Trimester 2 average)				
NO_2 (per IQR, 14.4 μg/m^3)	0.98 (0.96, 1.00)	0.89 (0.87, 0.91)	0.88 (0.86, 0.90)	0.88 (0.86, 0.90)
NO_X (per IQR, 37.3 μg/m^3)	0.98 (0.97, 1.00)	0.91 (0.89, 0.93)	0.90 (0.88, 0.92)	0.90 (0.88, 0.92)
$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.35 μg/m^3)	0.99 (0.98, 1.00)	0.92 (0.91, 0.94)	0.91 (0.89, 0.93)	0.91 (0.89, 0.93)
$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	1.00 (0.98, 1.01)	0.95 (0.93, 0.96)	0.93 (0.92, 0.95)	0.93 (0.92, 0.95)
$PM_{2.5}$ (per IQR, 3.6 μg/m^3)	0.93 (0.92, 0.95)	0.85 (0.83, 0.87)	0.85 (0.83, 0.87)	0.85 (0.83, 0.87)
PM_{10} (per IQR, 4.5 μg/m^3)	0.92 (0.91, 0.93)	0.83 (0.82, 0.85)	0.82 (0.81, 0.84)	0.82 (0.81, 0.84)
O_3 (per IQR, 19.1 μg/m^3)	1.00 (0.99, 1.02)	1.15 (1.11, 1.18)	1.15 (1.11, 1.18)	1.15 (1.11, 1.18)

Note: N for Trimester 1 exposures for preterm birth models is 578,382 live births, of which 33,712 are cases of preterm birth, and for Trimester 2 exposures is 577,161 live births, of which 32,491 are cases of preterm birth.

[a] Adjusted model covariates: Sex, Maternal age, Birth registration type, Tobacco expenditure (COA-level), Carstairs quintile (COA-level), Individual-level ethnicity, Season of conception, Year (linear term) and random intercept for MSOA.

[b] Additionally adjusted for noise as continuous per IQR, Day-time noise, $L_{Aeq,16hr}$ (per IQR, 3.5 dB), Night-time noise, L_{night} (per IQR, 3.9 dB).

Table 4
Odds of stillbirth associated with air pollutant exposure, in single-exposure and joint air pollutant-noise exposure models (OR, 95% CI).

Exposure	Stillbirth			
	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted + day-time noise[b] OR (95% CI)	Adjusted + night-time noise[b] OR (95% CI)
Air pollutants (Trimester 1 average)				
NO_2 (per IQR, 14.0 μg/m^3)	1.02 (0.97, 1.07)	0.93 (0.87, 1.00)	0.92 (0.86, 0.99)	0.92 (0.86, 0.99)
NO_X (per IQR, 36.7 μg/m^3)	1.01 (0.97, 1.06)	0.94 (0.88, 1.00)	0.93 (0.87, 0.99)	0.93 (0.87, 0.99)
$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.35 μg/m^3)	1.02 (0.98, 1.06)	0.96 (0.91, 1.00)	0.94 (0.89, 0.99)	0.94 (0.89, 0.99)
$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	1.04 (0.99, 1.08)	0.99 (0.94, 1.04)	0.98 (0.93, 1.04)	0.98 (0.93, 1.04)
$PM_{2.5}$ (per IQR, 3.2 μg/m^3)	0.97 (0.93, 1.02)	0.88 (0.82, 0.94)	0.87 (0.82, 0.93)	0.87 (0.82, 0.93)
PM_{10} (per IQR, 4.0 μg/m^3)	0.94 (0.90, 0.99)	0.84 (0.79, 0.88)	0.82 (0.78, 0.87)	0.82 (0.78, 0.87)
O_3 (per IQR, 17.6 μg/m^3)	1.04 (0.98, 1.09)	1.17 (1.07, 1.27)	1.17 (1.08, 1.27)	1.17 (1.08, 1.27)
Air pollutants (Trimester 2 average)				
NO_2 (per IQR, 14.4 μg/m^3)	1.05 (1.00, 1.10)	0.92 (0.86, 0.99)	0.90 (0.84, 0.98)	0.90 (0.84, 0.98)
NO_X (per IQR, 37.3 μg/m^3)	1.04 (1.00, 1.09)	0.93 (0.87, 1.00)	0.91 (0.85, 0.98)	0.91 (0.85, 0.98)
$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.35 μg/m^3)	1.04 (1.00, 1.08)	0.95 (0.90, 1.00)	0.93 (0.87, 0.98)	0.93 (0.87, 0.98)
$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	1.04 (1.00, 1.08)	0.99 (0.94, 1.04)	0.96 (0.91, 1.02)	0.96 (0.91, 1.02)
$PM_{2.5}$ (per IQR, 3.6 μg/m^3)	1.03 (0.98, 1.08)	0.92 (0.85, 0.99)	0.91 (0.85, 0.99)	0.91 (0.85, 0.99)
PM_{10} (per IQR, 4.5 μg/m^3)	1.04 (1.00, 1.08)	0.91 (0.86, 0.97)	0.90 (0.85, 0.96)	0.90 (0.85, 0.96)
O_3 (per IQR, 19.1 μg/m^3)	0.98 (0.93, 1.03)	1.20 (1.09, 1.32)	1.21 (1.10, 1.33)	1.21 (1.10, 1.33)
Air pollutants (Last 3 months average)				
NO_2 (per IQR, 14.4 μg/m^3)	1.05 (1.00, 1.10)	0.98 (0.91, 1.04)	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)
NO_X (per IQR, 37.0 μg/m^3)	1.04 (1.00, 1.09)	0.98 (0.92, 1.05)	0.98 (0.91, 1.04)	0.98 (0.91, 1.04)
$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.33 μg/m^3)	1.04 (1.00, 1.08)	0.99 (0.94, 1.03)	0.98 (0.93, 1.03)	0.98 (0.93, 1.03)
$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	1.04 (1.00, 1.08)	0.99 (0.94, 1.04)	0.98 (0.93, 1.03)	0.98 (0.93, 1.03)
$PM_{2.5}$ (per IQR, 3.6 μg/m^3)	1.03 (0.98, 1.08)	0.97 (0.91, 1.04)	0.97 (0.90, 1.04)	0.97 (0.90, 1.04)
PM_{10} (per IQR, 4.7 μg/m^3)	1.04 (1.00, 1.08)	0.98 (0.93, 1.04)	0.98 (0.92, 1.04)	0.98 (0.92, 1.04)
O_3 (per IQR, 17.9 μg/m^3)	0.98 (0.93, 1.03)	1.03 (0.95, 1.11)	1.03 (0.95, 1.11)	1.03 (0.95, 1.11)

Note: N for stillbirth models is 581,774, of which 3392 are cases of stillbirth, except for Trimester 2 average where N is 580,500, of which 2889 are cases of stillbirth.
[a]Adjusted model covariates: Sex, Maternal age, Birth registration type, Tobacco expenditure (COA-level), Carstairs quintile (COA-level), Individual-level ethnicity, Season of conception, Year (linear term) and random intercept for MSOA.
[b] Additionally adjusted for noise as continuous per IQR, Day-time noise, $L_{Aeq,16hr}$ (per IQR, 3.5 dB), Night-time noise, L_{night} (per IQR, 3.9 dB).

were no associations between stillbirth and Last 3 Months air pollutants when restricting to term (for which the Last 3 Months may represent a more comparable biological time window, predominantly Trimester 3, for both live and stillbirths) (Supplementary Table 8). Associations with noise changed little when excluding those exposed to rail and/or aircraft noise (Lday) > 50 dB (data not shown). There were some statistically significant interactions between exposures and ethnicity (for PTB and stillbirth) and Inner/Outer London (for PTB) (Supplementary Tables 9, 10 and 11), and one statistically significant interaction for deprivation (Carstairs) with Trimester $PM_{2.5\ traffic\ exhaust}$ for preterm birth (p = 0.04). Air pollutant exposure ORs for preterm birth were larger (in either elevated or 'protective' direction) for White ethnicity, compared to other ethnicities (Supplementary Table 9). 'Protective' associations with primary traffic-related air pollutants were limited to White and Other ethnicities (Supplementary Table 9). Last 3 months O_3 was inversely associated with risk of stillbirth for Other ethnicity babies, but otherwise there were no statistically significant associations within ethnic strata, although Last 3 months primary traffic-related air pollutant exposures tended towards 'protective' odds for White/Asian and increased odds of stillbirth for Black and Other ethnicity babies (Supplementary Table 10). Air pollutant associations were similar when stratified by Inner vs. Outer London. Higher noise was associated with elevated risks of PTB in Inner London, but not Outer London (Supplementary Table 11), and adjustment for air pollutants did not change this pattern.

4. Discussion

To our knowledge, this is the first study of stillbirth and long-term road traffic noise, and of cause-specific stillbirth in relation to traffic-related air pollution and O_3, and the largest investigating air and noise pollution jointly in relation to PTB. We find elevated risk of PTB and stillbirth (particularly asphyxia-related stillbirth) associated with increasing O_3 exposure during Trimesters 1 and 2. We found elevated risk of PTB and stillbirth associated with $PM_{2.5\ traffic\text{-}non\text{-}exhaust}$, but only after adjustment for O_3, but otherwise no evidence of increased risk associated with other primary traffic-related air pollutants or particulate matter. We found some associations between road traffic noise and PTB after adjustment for air pollution.

4.1. Comparison with prior studies

Many previous air pollution studies are limited by use of area-wide or semi-individual exposure assessment based on nearest monitor, which may not capture the spatial variability in exposure adequately, particularly within cities (Pedersen, 2016), and lead to Berkson error. More recent studies have tended to address this limitation by using spatial modelling approaches, although these have varied in spatio-temporal resolution (Klepac et al., 2018). There is considerable heterogeneity in findings from previous air pollution studies of PTB and stillbirth, and subsequent meta-analysis estimates (Klepac et al., 2018; Siddika et al., 2016). This may reflect, in part, the varied exposure assessment approaches used (Klepac et al., 2018) which is important to bear in mind when comparing with findings from our study which used a highly resolved spatio-temporal air pollution model on a 20x20m grid.

Given the large volume of literature on PTB and air pollution, we focus here on comparing our findings with the most comprehensive recent meta-analysis and with studies which have examined air pollution and noise jointly. Our finding of elevated risk of PTB associated with exposure to O_3 in Trimesters 1 and 2, is consistent with summary ORs (per 10 ppb O_3) from the most comprehensive recent meta-analysis (Trimester 1 OR 1.03 (1.01, 1.05) (N = 9 studies), Trimester 2 OR 1.12 (1.05, 1.19) (N = 6), Trimester 3 OR 1.01 (0.99, 1.03) (N = 4), pregnancy OR 1.03 (1.01, 1.04) (N = 5)) (Klepac et al., 2018). Of 5 studies not included in this meta-analysis which reported effect estimates for

Table 5
Odds of preterm birth and stillbirth associated with road traffic noise, in single-exposure and joint air pollutant-noise exposure models (OR, 95% CI).

Model	Preterm birth		Stillbirth	
	Day-time noise, $L_{Aeq,16hr}$ (per IQR, 3.5 dB) OR (95% CI)	Night-time noise, L_{night} (per IQR, 3.9 dB) OR (95% CI)	Day-time noise, $L_{Aeq,16hr}$ (per IQR, 3.5 dB) OR (95% CI)	Night-time noise, L_{night} (per IQR, 3.9 dB) OR (95% CI)
Unadjusted	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)	1.01 (0.99, 1.04)	1.01 (0.99, 1.04)
Adjusted[a]	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.01 (0.98, 1.03)	1.01 (0.98, 1.03)
Adjusted[a] + Trimester 1 NO_2 (per IQR) [b]	1.01 (1.00, 1.02)*	1.01 (1.00, 1.02)*	1.01 (0.99, 1.04)	1.02 (0.99, 1.04)
Adjusted[a] + Trimester 1 NO_X (per IQR) [b]	1.01 (1.00, 1.02)*	1.01 (1.00, 1.02)	1.01 (0.99, 1.04)	1.02 (0.99, 1.04)
Adjusted[a] + Trimester 1 $PM_{2.5\ traffic\text{-}exhaust}$ (per IQR)	1.01 (1.00, 1.02)†	1.02 (1.00, 1.02)†	1.02 (0.99, 1.04)	1.02 (0.99, 1.05)
Adjusted[a] + Trimester 1 $PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR) [b]	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)
Adjusted[a] + Trimester 1 $PM_{2.5}$ (per IQR) [b]	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.01 (0.99, 1.04)	1.01 (0.99, 1.04)
Adjusted[a] + Trimester 1 PM_{10} (per IQR) [b]	1.01 (1.00, 1.02)†	1.01 (1.01, 1.02)†	1.02 (1.00, 1.05)*	1.03 (1.00, 1.05)*
Adjusted[a] + Trimester 1 O_3 (per IQR) [b]	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)
Adjusted[a] + Trimester 2 NO_2 (per IQR) [b]	1.01 (1.00, 1.02)†	1.01 (1.00, 1.02)†	1.02 (1.00, 1.05)	1.02 (1.00, 1.05)
Adjusted[a] + Trimester 2 NO_X (per IQR) [b]	1.01 (1.00, 1.02)†	1.01 (1.00, 1.02)†	1.02 (1.00, 1.05)	1.02 (1.00, 1.05)
Adjusted[a] + Trimester 2 $PM_{2.5\ traffic\text{-}exhaust}$ (per IQR) [b]	1.02 (1.01, 1.03)§	1.02 (1.01, 1.03)§	1.03 (1.00, 1.05)*	1.03 (1.00, 1.06)*
Adjusted[a] + Trimester 2 $PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR) [b]	1.02 (1.01, 1.02)†	1.02 (1.01, 1.03)†	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)
Adjusted[a] + Trimester 2 $PM_{2.5}$ (per IQR) [b]	1.01 (1.00, 1.01)	1.01 (1.00, 1.02)	1.02 (0.99, 1.04)	1.02 (0.99, 1.04)
Adjusted[a] + Trimester 2 PM_{10} (per IQR) [b]	1.02 (1.01, 1.02)§	1.02 (1.01, 1.03)§	1.02 (1.00, 1.05)	1.02 (1.00, 1.05)
Adjusted[a] + Trimester 2 O_3 (per IQR) [b]	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)	1.02 (0.99, 1.04)	1.02 (0.99, 1.05)
Adjusted[a] + Last 3 Months NO_2 (per IQR) [b]			1.01 (0.99, 1.03)	1.01 (0.99, 1.04)
Adjusted[a] + Last 3 Months NO_X (per IQR) [b]			1.01 (0.98, 1.03)	1.01 (0.98, 1.04)
Adjusted[a] + Last 3 Months $PM_{2.5\ traffic\text{-}exhaust}$ (per IQR) [b]			1.01 (0.99, 1.04)	1.01 (0.99, 1.04)
Adjusted[a] + Last 3 Months $PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR) [b]			1.01 (0.99, 1.04)	1.01 (0.98, 1.04)
Adjusted[a] + Last 3 Months $PM_{2.5}$ (per IQR) [b]			1.01 (0.98, 1.03)	1.01 (0.98, 1.03)
Adjusted[a] + Last 3 Months PM_{10} (per IQR) [b]			1.01 (0.98, 1.03)	1.01 (0.98, 1.03)
Adjusted[a] + Last 3 Months O_3 (per IQR) [b]			1.01 (0.98, 1.03)	1.01 (0.98, 1.03)

Note: N for preterm birth models is 578,382 live births, of which 33,712 are cases of preterm birth, except where adjusted for Trimester 2 air pollutant exposures (N for preterm birth models is 577,161 live births, of which 32,491 are cases of preterm birth). N for stillbirth models is 581,774, of which 3392 are cases of stillbirth, except where adjusted for Trimester 2 air pollutant exposures (N for stillbirth models is 580,500, of which 2889 are cases of stillbirth). IQR values for Trimester 1 average air pollutants: NO_2 (per IQR, 14.0 μg/m^3), NO_X (per IQR, 36.7 μg/m^3), $PM_{2.5\ traffic\ exhaust}$ (per IQR, 0.35 μg/m^3), $PM_{2.5\ traffic\ non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3), $PM_{2.5}$ (per IQR, 3.2 μg/m^3), PM_{10} (per IQR, 4.0 μg/m^3), O_3 (per IQR, 17.6 μg/m^3). IQR values for Trimester 2 average air pollutants: NO_2 (per IQR, 14.4 μg/m^3), NO_X (per IQR, 37.3 μg/m^3), $PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.35 μg/m^3), $PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3), $PM_{2.5}$ (per IQR, 3.6 μg/m^3), PM_{10} (per IQR, 4.5 μg/m^3), O_3 (per IQR, 19.1 μg/m^3).
IQR values for Last 3 Months average air pollutants: NO_2 (per IQR, 14.4 μg/m^3), NO_X (per IQR, 37.0 μg/m^3), $PM_{2.5\ traffic\ exhaust}$ (per IQR, 0.33 μg/m^3), $PM_{2.5\ traffic\ non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3), $PM_{2.5}$ (per IQR, 3.6 μg/m^3), PM_{10} (per IQR, 4.7 μg/m^3), O_3 (per IQR, 17.9 μg/m^3).

[a] Adjusted for Sex, Maternal age, Birth registration type, Tobacco expenditure (COA-level), Carstairs quintile (COA-level), Individual-level ethnicity, Season of conception, Year (linear term) and random intercept for MSOA.

[b] Additionally adjusted for the air pollutant stated in the table above.

* $p \leq 0.05$.

† $p \leq 0.01$.

§ $p \leq 0.0001$.

Table 6
Odds of preterm birth associated with air pollutant exposures, in two-air pollutant models (OR, 95% CI).

Exposure window	Pollutant exposure 1	Pollutant exposure 2	Exposure 1 Adjusted[a] OR (95%CI)	Exposure 2 Adjusted[a] OR (95%CI)
Trimester 1	NO_2 (per IQR, 14.0 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	1.00 (0.97, 1.03)	1.15 (1.10, 1.19)
Trimester 1	NO_X (per IQR, 36.7 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	1.01 (0.98, 1.04)	1.16 (1.11, 1.20)
Trimester 1	$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.35 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	1.00 (0.98, 1.02)	1.14 (1.10, 1.18)
Trimester 1	$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	1.03 (1.01, 1.05)	1.18 (1.14, 1.22)
Trimester 1	$PM_{2.5}$ (per IQR, 3.2 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	0.96 (0.93, 0.98)	1.12 (1.09, 1.16)
Trimester 1	PM_{10} (per IQR, 4.0 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	0.90 (0.88, 0.92)	1.09 (1.06, 1.12)
Trimester 2	NO_2 (per IQR, 14.4 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	0.92 (0.89, 0.95)	1.07 (1.02, 1.11)
Trimester 2	NO_X (per IQR, 37.3 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	0.95 (0.92, 0.98)	1.09 (1.04, 1.14)
Trimester 2	$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.35 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	0.95 (0.93, 0.97)	1.08 (1.05, 1.12)
Trimester 2	$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	0.99 (0.97, 1.01)	1.13 (1.09, 1.18)
Trimester 2	$PM_{2.5}$ (per IQR, 3.6 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	0.87 (0.85, 0.89)	1.07 (1.04, 1.11)
Trimester 2	PM_{10} (per IQR, 4.5 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	0.84 (0.82, 0.85)	1.03 (1.00, 1.06)

Note: N for Trimester 1 exposures for preterm birth models is 578,382 live births, of which 33,712 are cases of preterm birth, and for Trimester 2 exposures is 577,161 live births, of which 32,491 are cases of preterm birth.

[a] Adjusted model covariates: Sex, Maternal age, Birth registration type, Tobacco expenditure (COA-level), Carstairs quintile (COA-level), Individual-level ethnicity, Season of conception, Year (linear term) and random intercept for MSOA.

Table 7
Odds of stillbirth associated with air pollutant exposures, in two-air pollutant models (OR, 95% CI).

Exposure window	Pollutant exposure 1	Pollutant exposure 2	Exposure 1 Adjusted[a] OR (95%CI)	Exposure 2 Adjusted[a] OR (95%CI)
Trimester 1	NO_2 (per IQR, 14.0 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	1.04 (0.94, 1.14)	1.20 (1.07, 1.35)
Trimester 1	NO_X (per IQR, 36.7 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	1.05 (0.96, 1.15)	1.22 (1.08, 1.37)
Trimester 1	$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.35 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	1.01 (0.96, 1.07)	1.18 (1.07, 1.31)
Trimester 1	$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	1.07 (1.01, 1.13)	1.25 (1.13, 1.38)
Trimester 1	$PM_{2.5}$ (per IQR, 3.2 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	0.90 (0.84, 0.97)	1.11 (1.02, 1.22)
Trimester 1	PM_{10} (per IQR, 4.0 μg/m^3)	O_3 (per IQR, 17.6 μg/m^3)	0.85 (0.80, 0.90)	1.07 (0.98, 1.17)
Trimester 2	NO_2 (per IQR, 14.4 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	1.05 (0.94, 1.17)	1.26 (1.09, 1.44)
Trimester 2	NO_X (per IQR, 37.3 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	1.05 (0.95, 1.17)	1.27 (1.10, 1.46)
Trimester 2	$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.35 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	1.01 (0.95, 1.08)	1.22 (1.08, 1.37)
Trimester 2	$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	1.07 (1.00, 1.14)	1.29 (1.15, 1.46)
Trimester 2	$PM_{2.5}$ (per IQR, 3.6 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	0.96 (0.89, 1.04)	1.18 (1.07, 1.31)
Trimester 2	PM_{10} (per IQR, 4.5 μg/m^3)	O_3 (per IQR, 19.1 μg/m^3)	0.95 (0.89, 1.01)	1.16 (1.05, 1.29)
Last 3 months	NO_2 (per IQR, 14.4 μg/m^3)	O_3 (per IQR, 17.9 μg/m^3)	0.98 (0.89, 1.08)	1.01 (0.90, 1.13)
Last 3 months	NO_X (per IQR, 37.0 μg/m^3)	O_3 (per IQR, 17.9 μg/m^3)	0.99 (0.91, 1.09)	1.02 (0.91, 1.14)
Last 3 months	$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.33 μg/m^3)	O_3 (per IQR, 17.9 μg/m^3)	0.99 (0.93, 1.05)	1.02 (0.92, 1.12)
Last 3 months	$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	O_3 (per IQR, 17.9 μg/m^3)	1.00 (0.94, 1.06)	1.02 (0.92, 1.13)
Last 3 months	$PM_{2.5}$ (per IQR, 3.6 μg/m^3)	O_3 (per IQR, 17.9 μg/m^3)	0.98 (0.91, 1.05)	1.02 (0.93, 1.11)
Last 3 months	PM_{10} (per IQR, 4.7 μg/m^3)	O_3 (per IQR, 17.9 μg/m^3)	0.99 (0.93, 1.05)	1.02 (0.94, 1.11)

Note: N for stillbirth models is 581,774, of which 3392 are cases of stillbirth, except for Trimester 2 average where N is 580,500, of which 2889 are cases of stillbirth.
[a] Adjusted model covariates: Sex, Maternal age, Birth registration type, Tobacco expenditure (COA-level), Carstairs quintile (COA-level), Individual-level ethnicity, Season of conception, Year (linear term) and random intercept for MSOA.

Table 8
Adjusted odds of cause-specific stillbirth (OR and 95% CI), associated with air pollutant or noise exposures, in single-exposure models.

Exposure	Congenital malformations-related stillbirth OR (95% CI)[a]	Asphyxia-related stillbirth OR (95% CI)[a]
Air pollutants (Trimester 1 average)		
NO_2 (per IQR, 14.0 μg/m^3)	0.93 (0.79, 1.10)	0.95 (0.81, 1.12)
NO_X (per IQR, 36.7 μg/m^3)	0.93 (0.80, 1.09)	0.95 (0.82, 1.11)
$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.35 μg/m^3)	0.98 (0.88, 1.10)	0.95 (0.85, 1.06)
$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	1.00 (0.89, 1.12)	1.01 (0.90, 1.13)
$PM_{2.5}$ (per IQR, 3.2 μg/m^3)	0.75 (0.64, 0.87)	0.92 (0.80, 1.06)
PM_{10} (per IQR, 4.0 μg/m^3)	0.74 (0.64, 0.85)	0.91 (0.80, 1.04)
O_3 (per IQR, 17.6 μg/m^3)	1.19 (0.97, 1.46)	1.22 (1.01, 1.49)
Air pollutants (Trimester 2 average)		
NO_2 (per IQR, 14.4 μg/m^3)	1.12 (0.93, 1.35)	0.84 (0.70, 1.00)
NO_X (per IQR, 37.3 μg/m^3)	1.09 (0.92, 1.30)	0.85 (0.72, 1.01)
$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.35 μg/m^3)	1.07 (0.94, 1.21)	0.87 (0.76, 0.99)
$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)	1.10 (0.98, 1.25)	0.92 (0.81, 1.04)
$PM_{2.5}$ (per IQR, 3.6 μg/m^3)	0.99 (0.81, 1.20)	0.84 (0.71, 0.99)
PM_{10} (per IQR, 4.5 μg/m^3)	0.98 (0.83, 1.15)	0.84 (0.73, 0.97)
O_3 (per IQR, 19.1 μg/m^3)	0.95 (0.74, 1.22)	1.22 (0.98, 1.52)
Air pollutants (Last 3 months average)		
NO_2 (per IQR, 14.4 μg/m^3)		0.98 (0.84, 1.14)
NO_X (per IQR, 37.0 μg/m^3)		0.97 (0.84, 1.13)
$PM_{2.5\ traffic\text{-}exhaust}$ (per IQR, 0.33 μg/m^3)		0.98 (0.87, 1.09)
$PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ (per IQR, 0.38 μg/m^3)		0.99 (0.89, 1.11)
$PM_{2.5}$ (per IQR, 3.6 μg/m^3)		0.98 (0.84, 1.14)
PM_{10} (per IQR, 4.7 μg/m^3)		0.98 (0.86, 1.12)
O_3 (per IQR, 17.9 μg/m^3)		1.03 (0.85, 1.24)
Day-time noise, $L_{Aeq,16hr}$ (per IQR, 3.5 dB)	1.00 (0.94, 1.05)	0.99 (0.94, 1.04)
Night-time noise, L_{night} (per IQR, 3.9 dB)	1.00 (0.94, 1.06)	0.99 (0.94, 1.05)

Note: N for congenital malformations-related stillbirth models is 578,945, of which 563 are cases of congenital malformations-related stillbirth (Wigglesworth code 1), except for Trimester 2 models (N for congenital malformations-related stillbirth models is 578,024, of which 413 are cases of congenital malformations-related stillbirth (Wigglesworth code 1)). N for asphyxia-related stillbirth models is 579,023, of which 641 are cases of asphyxia-related stillbirth (Wigglesworth codes 4 & 8A), except for Trimester 2 models (N for asphyxia-related stillbirth models is 578,145, of which 534 are cases of asphyxia-related stillbirth (Wigglesworth codes 4 & 8A)). Last 3 months average exposure not evaluated for congenital malformations-related stillbirth, because for this group of cases the Last 3 months overlaps more with Trimester 2 on average than it does with Trimester 3, and therefore is not considered informative as it represents a very different time window for cases compared to non-cases.
[a] Adjusted for Sex, Maternal age, Birth registration type, Tobacco expenditure (COA-level), Carstairs quintile (COA-level), Individual-level ethnicity, Season of conception, Year (linear term) and random intercept for MSOA.

Trimester 1 and/or 2 O_3 exposure, 4 reported elevated risk of PTB or reduced gestation (Han et al., 2018; Mendola et al., 2016; Olsson et al., 2012; Olsson et al., 2013), whilst Capobussi et al. (2016) reported no elevated risk in any trimester. Overall, the balance of evidence is in favour of an association between long-term O_3 exposure in the first two trimesters of pregnancy and increased risk of PTB, which is consistent with our findings.

For the other air pollutants we investigated (NO_2, NO_X, $PM_{2.5}$, $PM_{2.5\ traffic\text{-}exhaust}$, $PM_{2.5\ traffic\text{-}non\text{-}exhaust}$, $PM_{2.5}$, and PM_{10},) we did not find evidence of elevated risk, except for Trimester 1 $PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ after adjustment for O_3. All other ORs were < 1 (or null for Trimester 1 NO_2, NO_X, and $PM_{2.5\ traffic\text{-}exhaust}$ after adjustment for O_3). Our findings are somewhat in contrast to meta-analysis estimates suggesting null association or some elevated risk of PTB associated with PM_{10} (Trimester 1 OR 1.04 (1.01, 1.08), Trimester 2 OR 1.04 (0.98, 1.09), whole pregnancy OR 1.09 (1.03, 1.16) per 10 μg/m^3), $PM_{2.5}$ (Trimester 1 OR 1.03 (0.95, 1.11), Trimester 2 OR 1.10 (0.96, 1.27), whole pregnancy OR 1.24 (1.08, 1.41) per 10 μg/m^3), and NO_2 (Trimester 1 OR 0.99 (0.95, 1.03), Trimester 2 OR 1.02 (0.97, 1.08), whole pregnancy OR 1.05 (0.99, 1.11) per 10 ppb) (Klepac et al., 2018). Our findings are broadly compatible with the recent ESCAPE study of pooled birth cohorts across Europe (Giorgis-Allemand et al., 2017) (not included in the Klepac et al., 2018 meta-analysis) which found no evidence of elevated risk of PTB associated with NO_2, NO_X, $PM_{2.5}$ or PM_{10} for any time window including Trimesters 1 and 2 (virtually all ORs were < 1, but not statistically significant).

There is relatively little literature on environmental noise and PTB – a very recent systematic review and the only meta-analysis to date of road traffic noise and PTB found the evidence to be very low quality and not indicative of any significant effect of noise overall (OR 1.00 (0.79, 1.27) per 10 db(A)) or when limited to air pollution adjusted estimates (OR 1.00 (0.79, 1.26) per 10db(A)) (Dzhambov and Lercher, 2019). We found associations between road traffic noise and PTB after adjustment for air pollution, hinting at possible negative confounding by air pollution in our study area. Looking specifically at studies which examined both noise and air pollutants, no associations between long-term air pollution (NO_2, $PM_{2.5}$, PM_{10}) or noise during pregnancy and risk of PTB in single- or joint-exposure models in a French case-control study (N = 302 cases) (Barba-Vasseur et al., 2017), a population-based cohort study (N = 68,238) in Vancouver (Gehring et al., 2014; Hystad et al., 2014), or a study in the Tyrol Region of Austria/Italy (Dzhambov et al., 2019). N.B. all these studies included in the meta-analysis. The French study examined environmental noise overall, the Vancouver study focused on road traffic noise, and the Tyrol study examined rail/road noise. Consistent with our noise and O_3 findings, an ecological time-series study in Madrid (not included in the aforementioned meta-analysis) identified associations between PTB and O_3 (gestation week 12), $PM_{2.5}$ (week 17), diurnal noise (week 21), and night-time noise (week 36), but no associations with NO_2 or temperature, however it is severely limited by lack of adjustment for maternal lifestyle/socio-economic factors (Arroyo et al., 2016).

We observed elevated odds of stillbirth associated with Trimester 1 and 2 O_3, and for Trimester 1 and 2 $PM_{2.5\ traffic\text{-}non\text{-}exhaust}$ after adjustment for O_3. ORs below 1 for Trimester 1 $PM_{2.5}$ and PM_{10} remained after adjustment for O_3. The literature for stillbirth and air pollution is mixed. The only meta-analysis provides little convincing evidence that long-term exposure to NO_2, $PM_{2.5}$, PM_{10}, or O_3 is associated with stillbirth - whilst summary ORs were systematically elevated, virtually all confidence intervals included 1, despite including over 3 million births for NO_2, $PM_{2.5}$ and O_3 (Siddika et al., 2016). Comparing with more recent studies, our findings are broadly consistent with a US study which found chronic (first trimester and whole pregnancy) and acute exposure to O_3 were associated with increased stillbirth risk, but observed no consistent effects for NO_X, $PM_{2.5}$ or PM_{10} (Mendola et al., 2017). However, our findings contrast with a Chinese study which observed elevated risk of stillbirth associated with $PM_{2.5}$ (1st, 2nd, 3rd month, all trimesters, whole pregnancy) and PM_{10}, SO_2, NO_2, CO for Trimester 3, but no associations with O_3 (Yang et al., 2018). Another Chinese study observed elevated risk of stillbirth associated with $PM_{2.5}$ (all trimesters, whole pregnancy) and PM_{10} for Trimester 1, and O_3 for Trimester 1 and 3 (Zang et al., 2019), which is only consistent with our findings with respect to Trimester 1 O_3. Contrasting study findings could reflect differences in average exposure levels (generally much higher in the Chinese populations), exposure assessment methodology (both Chinese studies cited above used nearest monitor approach), and different gestational age cut-offs used for stillbirth definition/study inclusion e.g 20 (Yang et al., 2018), 23 (Mendola et al., 2017) and 28 weeks (Zang et al., 2019) compared with 24 weeks in the current study, which may influence the cause of stillbirth distribution (which likely differs by gestation) in the study populations.

Our findings for stillbirth appear to be driven, in part at least, by asphyxia-related stillbirth (O_3) and congenital malformations-related stillbirths ($PM_{2.5}$ and PM_{10}) respectively. Previous research on cause-specific stillbirth and air pollution is limited to one study on $PM_{2.5}$, which reported elevated risk of stillbirths due to all-causes, fetal growth and obstetric complications associated with pregnancy average $PM_{2.5}$, and stillbirths due to congenital malformations and fetal disorders with specific $PM_{2.5}$ constituents (Ebisu et al., 2018). Our findings are not directly comparable due to differences in stillbirth cause groupings and exposure windows analysed.

There are no published studies on stillbirth and long-term exposure to road traffic noise (or any other transportation noise), with which to compare our findings. One time-series study of late fetal death (includes late stillbirths) found elevated risk associated with specific 2nd and 3rd trimester gestational week exposures to air pollutants and temperature, but not noise, in Madrid (Arroyo et al., 2016).

Potential mechanisms via which O_3 could increase risk of PTB and stillbirth are oxidative stress and systemic inflammatory response (Kelly, 2003; Vadillo-Ortega et al., 2014), whilst those for noise are hypertension [which is associated with noise (van Kempen and Babisch, 2012), PTB (Bramham et al., 2014) and stillbirth (Flenady et al., 2011)]; disruption of endocrine/immune responses and placental blood flow induced by stress (Nieuwenhuijsen et al., 2017); or sleep disturbance (Palagini et al., 2014; World Health Organisation, 2011) e.g. via immune dysregulation (Blair et al., 2015). Elevated risks associated with O_3 or noise are unlikely to be mediated via fetal growth, as we previously found term low birth weight to be inversely associated with O_3 and little evidence for an independent exposure-response effect of noise on term low birth weight in the same study population (Smith et al., 2017). Nor are the findings for O_3 likely to reflect a common causal pathway for PTB and stillbirth, as associations between stillbirth and O_3 were similar when stratified by term/preterm births. The lack of any association between Last 3 Months air pollutant exposure and stillbirth may reflect that the underlying biological time window this exposure window represents differs for live vs stillbirths (which we acknowledge is a limitation, and makes interpretation difficult), and that the cause of death distribution likely varies by gestational age, and nearer to term, more stillbirths may be due to acute causes. Some apparently 'protective' effects of primary traffic-related air pollutants and particulate matter remained after adjustment of O_3, however these are not biologically plausible. A large number of statistical tests were carried out (examining various exposure indices, at various time windows during pregnancy, for multiple outcome measures) which increases the possibility of a Type I error (i.e. falsely rejecting the null hypothesis due to chance), so it is possible that some apparently statistically significant findings could be statistical artefact. Other possible explanations could be a healthy survivor effect, i.e. if exposure is positively associated with miscarriage, then prevalence of the most susceptible fetuses in the population at risk (after 24 weeks gestation) may be inversely related to exposure. For example, this could explain the 'protective' effects observed for congenital malformation-related stillbirths in relation to Trimester 1 $PM_{2.5}$ and PM_{10}, if the most severe congenital

malformations lead to miscarriage early in pregnancy. Previous research on air pollution and miscarriage is limited, but associations with traffic density and ambient $PM_{2.5}$, SO_2, O_3, CO, and correlations with ambient NO_2, PM_{10} and $PM_{2.5}$ have been reported (Enkhmaa et al., 2014; Green et al., 2009; Zhang et al., 2019). Residual confounding could also be an explanation, e.g. if hospitals located in high air pollution areas have more effective policies to reduce PTB and stillbirth, or if in lower pollution areas there are more medically-induced preterm births. We did not have information on spontaneous vs. medically-induced PTB to investigate this, but did control for unmeasured spatial confounding by including a random effect for small area in all models. We considered whether differential exposure measurement error could bias the results and, specifically, induce spurious 'protective' effects. Exposure measurement error may differ by age/deprivation, as younger, less well off mothers are more likely to move address during pregnancy (Tunstall et al., 2010). However, for this to induce spurious 'protective' effects those younger/more deprived mothers would have to be systematically moving from areas of higher exposure to lower exposure to NO_X, NO_2, $PM_{2.5}$, PM_{10}, and we have no reason to believe, or evidence to prove that such systematic movement by exposure is occurring - on the contrary, if anything, it is more plausible that more deprived mothers would be more likely to move to a more highly polluted area. Differential exposure measurement error could also vary according to daily mobility patterns, e.g. those who work/commute may have greater exposure measurement error than those who do not, and this could potentially interact with a 'healthy worker effect'. However, for this to induce spurious 'protective' effects those who work/commute would have to be systematically exposed to higher levels of NO_X, NO_2, $PM_{2.5}$, PM_{10} at their commute/work locations vs. their home address. Again, we have no reason to believe, or evidence to prove that such systematic movement by exposure is occurring, and in our opinion it is highly unlikely that differential exposure measurement error explains the apparent 'protective' effects. Findings of increased risk of PTB associated with increasing road traffic noise were only evident in models adjusted for certain primary traffic-related pollutants/PM_{10}, i.e. once the negative confounding of the apparent 'protective' effect of these air pollutants had been adjusted for. Given that those 'protective' effects are not biologically plausible, and are difficult to explain, by extension the findings of elevated risk of traffic noise when adjusted for these air pollutants should be interpreted cautiously.

The single statistically significant interaction observed between exposure and deprivation (Carstairs) may well reflect artefact. However, in models stratified by ethnicity we observed that the 'protective' associations for PTB tended to be strongest in the White group, as did the elevated risk associated with O_3; and that the 'protective' associations with primary traffic-related air pollutants were limited to White and Other ethnicities - the presence of a pattern suggests that the interactions are less likely to represent artefact. A pattern is not so clear for Last 3 Months exposures and stillbirth, stratified by ethnicity, but almost all the associations are not statistically significant. It is possible that there could be differential residual confounding patterns specific to particular ethnic groups, that could explain the effect modification. Associations between some air pollutants/noise and PTB differed between Inner and Outer London, however this is unlikely to be explained by residual confounding as risk of PTB did not differ between Inner and Outer London, so these may represent artefact.

4.2. Strengths and limitations

Strengths and limitations of our exposure assessment have been discussed in detail elsewhere (Smith et al., 2017), so they are outlined briefly here. This study benefits from highly spatially resolved exposure modelling with common traffic data inputs into both air pollutant and noise models, and exposure estimates assigned at address level. However, the accuracy of individual exposure assessment will be influenced by measurement error, one source of which may be daily/residential mobility, which we could not account for. Residential mobility during pregnancy in the UK is estimated to be 16% (Tunstall et al., 2010). However, reassuringly, analysis of the ALSPAC cohort in Bristol, UK, found that PM_{10} exposure estimates varied little on average (< 5%) when comparing exposure estimates based on full residential history during pregnancy vs those based on address at birth (Fecht et al., 2019). There could be some air pollution exposure misclassification close to sources, where primary pollutants gradients are steep, however only a small proportion of maternal residences were close to a major road, and key demographic factors differed little according to living close to a major road. $PM_{2.5}$ and PM_{10} were predicted slightly more accurately than NO_2 and NO_X, but for all these pollutants model bias was in the same direction (over-prediction), except for O_3 which under-predicted (reflecting the positive NO_2 bias). The directions of model bias would suggest that we may underestimate the true effect size for NO_X, NO_2, $PM_{2.5}$, PM_{10}, and overestimate the true effect size for O_3. Due to the constant for traffic on minor roads, the noise model is likely to have over- and under-estimated noise on some minor roads, but any bias due to this is not spatially patterned (Gulliver et al., 2015). Use of all birth registration data avoided selection bias. In addition to area-level deprivation and tobacco expenditure, we also adjusted for birth registration type which relates to qualifications, housing and smoking at individual-level (Graham, 2007) and thus adjusts for these by proxy. We cannot exclude the possibility of residual confounding by maternal/passive smoking, but previous research suggests individual-level adjustment for behavioural factors such as maternal smoking had little influence on the association between air pollution and PTB (Ritz et al., 2007). We did not adjust for temperature other than by adjusting for season, but where studies have examined both meteorological factors and air pollutants in relation to PTB/stillbirth, no evidence of air pollutant-temperature interaction has been reported (Avalos et al., 2017; Basu et al., 2010; Basu et al., 2016), nor significant confounding of the associations for temperature by air pollutants ($PM_{2.5}$, NO_2, SO_2, O_3, CO) (Avalos et al., 2017; Basu et al., 2010; Basu et al., 2016; Lee et al., 2008). We did not have data on pre-pregnancy BMI, so could not adjust for this. We were not able to examine spontaneous vs. medically induced PTB, thus limiting our ability to distinguish aetiologies.

5. Conclusions

This study suggests that exposure to higher levels of O_3 and primary traffic non-exhaust related $PM_{2.5}$ during pregnancy may increase risk of preterm birth and stillbirth. Our findings suggesting a possible relationship between long-term traffic noise and increased risk of preterm birth have not previously been reported in the literature. These findings strengthen the body of evidence for important public health impacts of ambient O_3, particulate matter, and noise in early life, which may have life-course consequences. Reduction of ambient O_3 to protect human health is complex, as it requires control of precursor compounds at local, regional and global level. At the urban scale, implementation of policies to reduce NO_X emissions from traffic to protect human health, e.g. the Ultra Low Emission Zone in London, could also have the unintended consequence of increasing O_3-related health impacts in early life, if causal, as NO_X titration-driven suppression of O_3 is reduced, and urban O_3 levels increase. Thus, the complex interrelationships between these compounds in our urban environments need to be carefully considered by policy makers to ensure overall net improvements in public health long term.

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Declaration of Competing Interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105290.

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